

10151 K/05 B07 BEEC 10.07.81
BEECHAM GROUP PLC
10.07.81-GB-021302 (19.01.83) A61k-09/20 A61k-47
Tablets of poorly compressible me- ment - contg. plasticiser to allow compression to be effected us...g conventional pressure

C83-009932

D/S:E(CH DE FR GB IT LI NL)

A tablet comprises a poorly compressible ingredient (I) and a plasticiser (II) incorporated into the tablet body.
Pref. (I) is a high dose medicament which represents at least 50 wt.% of the tablet; (II) is propylene glycol, liq. polyethylene glycol, glycerine, hexylene glycol, 1,2,6-trihydroxyhexane, solketal or diethyl phthalate and represents 0.1-2 wt.% of the tablet; and the tablet further includes 0.1-10 wt.% of binder, esp. 2-5 wt.% of water-soluble binder.

ADVANTAGE

Inclusion of (II) greatly increases the strength of the tablets formed at conventional compression pressures, greatly decreases their friability, but at the same time does not have a detrimental effect on their disintegration.

DETAILS

The binder is pref. a water-sol. material such as PVP,

B(4-C3C, 7-A4, 10-E4C, 10-G2, 12-M11) 5 053

gelatin, methyl hydroxyethyl cellulose, hydroxypropyl methyl cellulose or hydrolysed gelatin. Alternatively, a water-insol. material such as ethyl cellulose can be used to give a sustained release tablet.

The tablet is formed by mixing (I) and (II) prior to compression, and then compressing the mixt. Pref. (II) is added to a soln. of binder, the resultant soln. is added to (I) and the obtd. wet mix is formed into a dry powder/granulate conventionally, e.g. by wet granulation, spray granulation or spray drying. The obtd. powder or granular prod. is then compressed into tablets.

EXAMPLE

Paracetamol (476.5g) and Explotab (RTM; sodium starch glycollate; disintegrant) (10g) were blended in a tumbler mixer for 5 mins. Kollidon 90 (RTM; polyvinylpyrrolidone; binder) (10g) was then added as an 8% w/v aq. soln which also contained 1 g of propylene glycol. The resultant mixt. was mixed in a planetary mixer for 10 mins., wet screened through a 1.7 mm screen, dried at 50°C overnight and dry screened through a 1.0 mm screen. A 1000-200 µm sieve cut of the granules was blended with 0.5 wt.% Mg stearate and compressed into 200 mg tablets at conventional pressures of 30-150 MN/m². (13pp914).

EP/ISR:No Search Report.

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53 K/05 B05 ANAL-09.07.81
ANALYT RES PHARM PT *EP--70-131
08.04.82-AU-003542 (+009682) (19.01.83) A61k-31/67 C07f-09/38

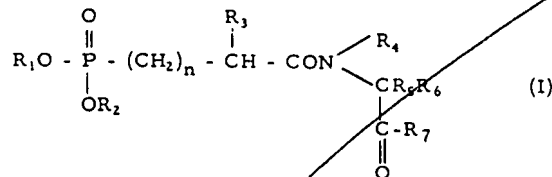
Antihypertensive phosphono:alkanol:amino acid cpds. - esp. useful for reduct. of angiotensin related hypertension

C83-009934

Intermediate priority: 13.11.81-AU-001560.

D/S: E(CH DE FR GB IT LI SE).

Phosphonoalkanoilamino acid cpds. of formula (I) and their pharmaceutically acceptable salts, are new:



(R₁, R₂ and R₃ are each H, opt.substd. lower alkyl, lower alkenyl, or opt.substd. aryl or aralkyl; n 0 or 1; and

B(5-B1E, 5-B1F, 5-B1G, 12-A1, 12-A6, 12-F5, 12-G1, 12-G7) 6 054

(a) R₄ is H, lower alkyl or phenyl-lower alkyl; R₅ and R₆ are each H, opt.substd. lower alkyl, or aryl; and R₇ is -OR₈, -NR₉ (sic) or -SR₁₀ where R₈ and R₁₀ are each H, lower alkyl or opt.substd. aryl or aralkyl, and R₉ is H, OH, lower alkyl or the residue of an α-amino acid; or
(b) R₄ and R₅ together form an opt.substd. bridge of 2-4 atoms of C or C with O, N or S; and R₆ and R₇ are as in (a); with the proviso that when R₃ is H, n is 0, the heterocyclic ring is an unsubstd. pyrrolidine, R₆ is H and R₇ is OR₈, at least one of R₁, R₂ and R₈ is opt.substd. aryl; or
(c) R₅ and R₆ are such as to form an α-amino acid side chain so that N(R₄)CR₅R₆COR₇ is an α-amino acid residue; with the proviso that (i) when R₃ is H and n is 0, the residue is not alanine, aspartic acid, glutamic acid, glycine or phenylalanine, and (ii) when R₃ is H and n is 1, the residue is not aspartic acid; or
(d) R₅ and R₆ are part of a 3-6C cycloalkyl ring; and R₄ and R₇, where appropriate, are as in (a)).

USES/ADVANTAGES

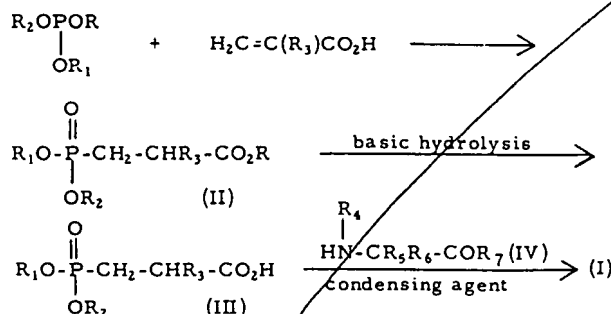
(I) are antihypertensive agents, esp. useful for reduction of angiotensin related hypertension. They may also be

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useful as antibacterial, anticancer and antiviral agents. The pref. (I) (in which R₇ is OR₈) are angiotensin converting enzyme inhibitors which are superior to mercapto-alkanoyl amino acid inhibitors since they lack the toxicity associated with the SH gp. (I) are more stable towards hydrolysis than known N-phosphorylated dipeptides and related cpds. Antihypertensive doses are e.g. 0.5-500 mg/kg/day, pref. in 2-4 units. Parenteral admin. is pref.

PREPARATION

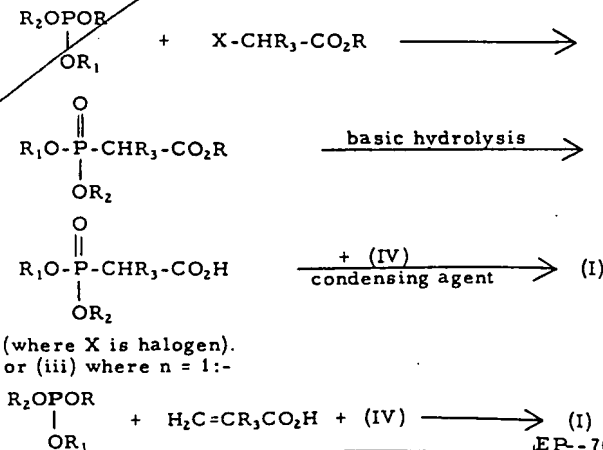
(i) where n = 1:-



(where R is lower alkyl, aryl or aralkyl).

Opt. (III) is converted to the acid chloride before amide formation.

(ii) where n = 0:-



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